PCT/ SE 03 / 0 0 2 8 4

PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

Intyg
Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

PATENT- OCH REGISTRERINGSVERKET • PATENT- OCH REGISTRERINGSVERKET

(71) *Sökande* *Jostra AB, Lund SE*
Applicant (s)

(21) *Patentansökningsnummer* *0200579-1*
Patent application number

(86) *Ingivningsdatum* *2002-02-25*
Date of filing

Stockholm, 2003-02-25

För Patent- och registreringsverket
For the Patent- and Registration Office

Lina Oljeqvist

Avgift
Fee

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

DEVICE AND METHOD FOR THROMBOLYSIS

Technical field

The present invention relates to the field of medical technology, specifically to devices and methods for correcting and treating of circulatory disturbances resulting from thrombosis.

Background

Thrombosis is a condition where a thrombus or blood cloth is obstructing or blocking the normal flow of blood trough a vessel. Thrombosis in an artery in an extremity can result in that said extremity has to be amputated.

The treatment of thrombosis is traditionally medical or surgical. Known methods for medical treatment is relatively inexpensive but is mainly a preventive type of treatment, involving oral drugs preventing thrombus build-up, and intravenous drugs both of the preventing thrombus build-up type and the thrombolytic type. Surgical treatment on the other hand, is mainly for treating acute thrombosis, and known methods tend to be relatively expensive.

There is a need for a more cost effective, efficient method for treating in the first place acute thrombosis.

WO 01/70325 to Kokish et al., shows an emboli protection system that provides one or more inflatable blocking baloons, introduceable into a blood vessel, for isolation of a section of said vessel to prevent the migration of emboli from the section during an interventional procedure, and fluid infusion and evacuation ports for flushing emboli from the isolated section. The blocking baloons can be perforated to provide the infusion ports, and thrombolytic inflation fluid may be used to break down and dissolve thombus and plaque in the isolated portion of the blood vessel.

US 4,540,399 to Litzie et al., shows a closed emergency heart bypass system for extra-corporeal blood circulation using few components. The components include a non-occlusive blood pump aspirating venous blood from an appropriate cannula for introduction to an oxygenator and a bubble-trapping device followed by return to a patient's body via an arterial cannula. Tubing interconnects the components and a bypass loop selectively joins the tubing adjacent to the venous and arterial cannulas for air displacement during initial pump priming and tube purging.

In an article to Mumme (Fortschr. Med. 113. Jg (1995), Nr. 13 A. Mumme, Fibrinolytikaperfusion) is described a method for hyperthermal fibrinolytic perfusion in an isolated extremity where a heart-lung machine is used to provide circulatory energy.

Summary

The present invention relates to a apparatus and method for thrombolytic (blood cloth dissolving) treatment of diagnosed thrombosis in an extremity. The invention is based on the idea to isolate the extremity from the rest of the system circulation and circulate separately in said extremity a liquid capable of being oxygenated and also capable of containing a potent fibrinolytic agent in order to rapidly dissolve the thrombosis. A basic apparatus comprises:
- compressing means devised for compressing a proximal end of the extremity so that essentially all vessels passing a cross section of said extremity become compressed - an incompressible arterial catheter, devised to withstand a compressing force generated by said compressing means, without collapsing;
- an incompressible venous catheter, likewise devised to withstand a compressing force generated by said compressing means, without collapsing;
- a fluid circulation loop, having a first end connectable to said arterial catheter, and a second end connectable to said venous catheter;
- pump means for providing circulatory energy substituting heart function;

This apparatus is useable for flushing the blood circulatory subsystem of an extremity by introducing said catheters into a main artery and vein of said extremity, in a distal direction, such that compressing means can be applied around the extremity distal to the entry site of said catheters, but proximal to the free ends of said catheters. By free ends is here meant those ends of the incompressible catheters not connected to the fluid circulation loop.

The compressing means are devised to, when applied on the outside of an extremity, exert a minimum inward pressure, said pressure being sufficient to shut off the blood flow through said cross-section, and wherein said catheters, arranged to pass through this cross-section, are devised to sustain said pressure, making it possible to access the blood vessels normally supplying the isolated extremity with blood, from a region of the patients body that resides outside said isolated extremity.

A major advantage of the present invention over known methods to isolate an extremity, such as the one described by Mumme, is the possibility to perform thrombolysis without having to open up a surgical wound, but rather to perform thrombolysis with interventional radiology technique (Seldinger technique) where the vessels are accessed from the inguinal area.

An other advantage of the present invention is that all vessels in an extremity can be treated, not only the ones having a luminal diameter great enough for lodging a catheter as compared to e.g. WO 01/70325, where balloons are used to block the blood flow. The present invention is also advantageous over a system with one

proximal venous balloon and one proximal arterial ballon in that such a system would not prevent the fibrinolytic agent from entering the rest of the circulatory system. This because of collateral flow in other vessels than the ones with balloons. Other advantages includes performance in condition with local anaestesia, ease of de-airing the perfusion circuit including catheters, possibility to rise the isolated extremity and change the contaminated fluid without disconnecting any part of the circuit, possibility to inject contrast solution, and do intervention with mechanical means during treatment.

Suitably, the above mentioned fluid circulation loop comprises:
-oxygenation means devised to oxygenate a fluid passing through substituting lung function;
- fluid reservoir means devised for providing volume buffering and bubble trapping capabilities
- filtering means devised for removing debris, such as partly dissolved clots
– shunt means for facilitating priming and de-airing of the fluid circulation loop and the catheters.
– heat providing means devised to add caloric energy and control the temperature of the circulating fluid.

Brief description of the Drawings

Figure 1 shows a system overview of an apparatus according to an embodiment of the invention;

Figure 2 shows an overview of and extremity treated using a apparatus according to an embodiment of the invention;

Figure 3 shows a reinforced catheter for introduction into a patient's extremity, in accordance with an embodiment of the invention; and

Figure 4 shows a control unit for controlling parameters such as temperature, oxygen saturation and fluid pressure in the isolated extremity, in accordance with an embodiment of the invention

Description

Figure 1 shows schematically an embodiment of a apparatus according to the invention.

A pump unit 101 is aspirating liquid, which can be venous blood or an artificial solution, from a venous reservoir. Further the pump 101 is connected via a first liquid transporting conduit 102 to an inlet 105 of a heat exchanger unit 103. Said heat exchanger unit 103 is at its outlet 104 connected to an inlet 106 of an oxygenator unit 108. An outlet 110 of said oxygenator unit 108 is connected via a

second liquid transporting conduit 112 to an inlet 115 of a first arterial Y-connector 114.

The first arterial Y-connector 114 is provided with a shunting outlet 117 and a mainstream outlet 116.

The mainstream outlet 116 of the first arterial Y-connector is connected, via a conduit with an arterial pinch clamp 118, to a second arterial Y-connector 120 having a mainstream inlet 121, an auxiliary inlet 122 and a mainstream outlet 123.

The auxiliary inlet 122 is connected to an interventive Y-connector 125 for making it possible to introduce instruments in the patient.

The mainstream outlet 123 of the second arterial Y-connector is connected to a first port 128 of an arterial three-way valve 127 which is suitable for giving contrast injections via a second port 130. A third port of the arterial three-way valve is connected via an arterial trunk conduit 132 to the patient's arterial catheter 202.

On the venous side, blood or liquid coming from the patient via a venous catheter 201 passes a venous front conduit 140. Said venous front conduit 140 is provided with a venous pinch clamp 142 and connected to a mainstream inlet 144 of a venous Y-connector 143. A shunt inlet 145 of said venous Y-connector is connected to the shunting outlet 117 and the first arterial Y-connector 114 via a shunt conduit 150 having a shunt pinch clamp 152. The venous Y-connector 143 is also provided with a mainstream outlet 146, which is connected to a first port 156 of a supplementary Y-connector 155 via an intermediate venous conduit 154.

A second port 157 of the supplementary Y-connector 155 is connected to a venous reservoir 180 with an integrated filter 162 via a filter conduit 160 with a filter pinch clamp 161. A third port 158 of the supplementary Y-connector 155 is connected to a collecting bag 159 via a collecting conduit 170 with a collecting pinch clamp 171.

After passing though the integrated filter 162 the liquid is collected in the venous reservoir 180, said venous reservoir has a prime port 181 for connecting a priming liquid bag 183 via a priming conduit having a priming pinch clamp 184.

The venous reservoir 180 is provided with an outlet 186 connected to a first port of a central Y-connector 188, via a conduit provided with a venous outlet pinch clamp 187. A second port of said central Y-connector is connected via a supply conduit 190 with a supply three-way valve 191 to a first port of a liquid selection three-way valve 192. A second and a third port of said liquid selection three-way valve is connected to a washing liquid supply 195 and a blood supply 196.

A third part of the central three-way valve is connected to an inlet 197 of the pump unit 101. The pump is controlled by the control unit 199.

A preferred embodiment of the method according to the invention includes preparing a patient for the treatment by e.g. administering to him or her local

anesthetics. Members for the performance of the treatment comprises a catheter set, a tube set, a pump, a heat exchanger, an oxygenator, a venous reservoir with an integrated filter and some liquids as described above and will be further explained below. In short the following steps are included: priming and de-airing the tube and pumps, catherisation of the patient, de-airing of the catheters, oxygenating and circulating the extremity during the act of thrombolysis, engagement of thrombolysis, replacing of the thrombolytic liquid with blood or a washing solution and then with blood, stopping the pump and decatherisation. Below these steps are described in greater detail.

Priming of the tube and pump

Priming the tube and pump comprises the following steps:

- Closing of the arterial and venous pinch clamps 118 and 142, opening of the shunt pinch clamp 152 for the shunt 150.
- Closing of the venous reservoir outlet pinch clamp 187.
- Filling of the venous reservoir with a suitable liquid e.g. Ringers solution + Mannitol + blood + some tissue recovery agents
- Opening of the venous reservoir outlet pinch clamp 187 and the central three-way valve in the venous reservoir outlet branch 186 to the air, enabling air to pass out from the tube system.
- Closing of the three-way valve 191 when air free liquid is pouring out
- Closing of the pinch clamp 171 to the collecting bag 159.
- Starting the pump 101 in order to evacuate air from the oxygenator 108, heat exchanger 103 and the tube set.
- Let the pump 101 run for a while. The system is now primed.

Catheterisation

Catheterisation comprises the following steps:

- Prepairing the patient with e.g. local anesthetics.
- Catheterisation of the inguinal artery and the inguinal vein in the extremity that is to be treated. (The catheters are described in a separate section below.
- The arterial catheter is connected to the arterial front tube 132 and the venous catheter is connected to the venous front tube 140.
- Applying a tourniquet for achieving a bloodless field. The distal end of the tourniquet should be applied approximate of the distal end of the catheters.

De-airing of the catheters

The de-airing process for the catheters comprises the following steps:

- Opening of the arterial pinch clamp 118 and letting air be transported into the venous reservoir 180, this will take just a short moment.
- Closing of the arterial pinch clamp 118.
- Opening of the venous pinch clamp for a short moment and letting air pass to the venous reservoir 180.

Circulation and oxygenation

Circulation and oxygenation comprises the following steps:

- Shutting the pump 101 off.
- Closing of the shunt pinch clamp 152 on the shunt conduit.
- Opening of the arterial pinch clamp 118.
- Slowly starting of the pump 101.
- Opening of the venous pinch clamp 142.
- Increasing the flow and regulating the flow until acceptable pressure has been achieved and the constant level in the venous reservoir 180 is achieved (as small systemic in-flow can be tolerated, but not the opposite). The step of regulating the flow and pressure can be accomplished be the use of a level sensor, sensing the level in the venous reservoir. Sensor can signal to decrease pump speed if level in reservoir decreases. Suitable sensor types include, fotocell, pressure sensor, ultrasound, and capacitive sensors, capable of measuring the hight of the liquid in the reservoir 180.

Thrombolysis

Thrombolysis comprises the steps of:

- Adding to the liquid in the venous reservoir 180 an amount of a thrombolytic agent such as steptokinase, Actilyse® or the like.
- Letting the pump 101 work for a couple of minutes.
- Checking the result of the operation/thrombolysis by injecting a contrast liquid in the second port 130 of the arterial three-way valve 127, and performing angiography.

Terminating the treatment

The termination of the treatment comprises the following steps:

- Stopping of the pump 101.
- Shutting off of the pinch clamp 187 between the venous reservoir 180 and the arterial pump 101.
- Opening of the three-way valve 191 in the supply conduit 190 to the

selected washing fluid. Different types of washing fluid includes colloid solutions, blood, Ringer's solution. Coloured additives such as Evans blue can be added for easier deciding when extremity is washed from thrombolytic agent.

- Shutting the incoming venous tube 160 to the venous reservoir 180 between the reservoir inlet and the Y- connector 155.
- Opening the pinch clamp 171 to the collecting bag 159.
- Starting the pump 101.
- Keep the pump 101 running until washing fluid is coming from the venous front conduit.
- Stopping the pump 101.
- Connecting the liquid solution three-way valve 192 to the blood bag 196.
- Starting the pump 101 again.
- Keep the pump 101 running until blood is coming from the venous front conduit 190.
- Let or roll down a bit of the tourniquet until the valve for letting the pressure out of it is seen.
- Release pressure from tourniquet.
- Remove tourniquet.
- Decatherisation, (reversed catherisation).
- Compressing the skin at the insertion sites, to avoid post-treatment bleedings.
-

Figure 2 shows an overview of an extremity that is in the process of being treated using a apparatus according to an embodiment of the invention. The arterial front tube 132 is connected to the arterial catheter 202 which is applied into the femoral artery. The venous front tube 140 is connected to the venous catheter 201 which is applied in the femoral vein. A pressure means in the form of a tourniquet 205 with a height h is applied over a proximal portion 207 of the patient's extremity.

Figure 3 shows a detailed view of the arterial catheter 202, the venous catheter having the same principal appearance. The catheter 202 has a first end 301, a second end 303 and a reinforced section 305 with a length L. Said reinforced section 305 is devised to make the catheter withstand an outside pressure, i.e giving it structural strength so that it will not collapse when exposed to the pressure of the pressure means 205. The reinforcement can be a metal or composite wire or coil 310 embedded in the catheter wall. The second end 303 has means for being able to connect to the arterial front tube

Figure 4 shows a control unit 401 for controlling parameters such as temperature, oxygen saturation and fluid pressure in the isolated extremity. The control unit comprises a input unit 410 for receiving signals from sensors sensing system parameters in the system such as levels, temperatures, pressures and speeds. The input unit 410 is connected to a processor 412. Said processor 412 processes said parameters and shows them on a display 414. Operator input is provided via a keyboard 416. A memory unit 418 is provided for storing computer program instructions for instructing the processor 412 and for storing control parameters input from the keyboard 416. The control unit also comprises an output unit for distributing control signals to the pump 101, and in alternative embodiments also to the heating means 103 and the oxygenator 108 and electronically manoeuvred valves replacing some of the pinch clamps.

CLAIMS

1. An apparatus for treatment of a patient's extremity **characterised in** that said apparatus comprises:
- a tourniquet-shaped compressing means (205) having a predetermined height (h)
- an incompressible arterial catheter (202) having an elongated section (305) that is reinforced to withstand an outside pressure and where said section have a length (L) that is greater than the height (h) of the compressing means (305)
- an incompressible venous catheter (201) likewise having an elongated section (305) that is reinforced to withstand an outside pressure and where said section have a length (L) that is greater than the height (h) of the compressing means (305)
- a fluid circulation loop, having a first end (132) connectable to said arterial catheter (202), and a second end (140) connectable to said venous catheter (201);

2. The apparatus as recited in claim 1, **characterised in** that said apparatus further comprises:
- pump means (101) devised for circulating a fluid in said fluid circulating loop and said catheters;

3. An apparatus for the treatment of thrombosis in a patient's extremity **characterised in** that said apparatus comprises:
- compressing means (205) with a height (h), applicable around said extremity devised to compress a section of said extremity and thereby isolate the circulation and prevent a leakage of a fluid, that can be blood or a therapeutic liquid, from said extremity to the rest of the patients circulation;
- catheters (201, 202), having a reinforced section (305) with a length (L) greater than the height (h) of said compressing means (205), devised for being introduced in an artery and in a vein having connection to said extremity;
- a fluid circulation loop, having a first end (132) connectable to said arterial catheter (202), and a second end (140) connectable to said venous catheter (201);for transporting blood and said therapeutic liquid to and from the patient via said catheters.

4. An apparatus as recited in claim 3, **characterised in** that said apparatus further comprises pump means (101) devised for pumping blood and said therapeutic liquid.

5. The apparatus as recited in claim 4, **characterised in** that said therapeutic liquid have a composition that makes said liquid possible to oxygenate and that said apparatus also comprises an oxygenator unit (108) capable of oxygenating blood and said therapeutic liquid for the purpose of supplying said extremity with oxygen during a prolonged period of time.

6. The apparatus as recited in claim 5, **characterised in** that said apparatus further comprises heating means (103) connected in the fluid circulation loop, with the purpose of warming the fluid.

7. The apparatus as recited in claim 4, **characterised in** that said apparatus comprises a control unit (199, 401) with a input unit (410) for a number of input signal lines and a output unit (411) for a number of control lines devised for controlling a number of process parameters including fluid pressure and temperature, oxygen saturation, and the flow speed of said fluid.

8. A apparatus as recited in claim 5, **characterised in** that said circulatory unit comprises a venous reservoir with an inlet for receiving fluid coming from the patient, and an outlet connected to the pump means (101) for recycling the fluid to the patient.

9. The apparatus as recited in claim 6, **characterised in** that it comprises a level sensor capable of measuring the height of fluid in the venous reservoir (180)

10. The apparatus as recited in claim 7, **characterised in** that said control unit (199, 401) comprises a display (414) devised for displaying trend curves and the level of fluid in the venous reservoir and time of treatment

11. The apparatus as recited in claim 8 where said tube set comprises a shunt connection (150) between an arterial and a venous part of the tube set, said shunt connection (150) having a valve means (152) enabling the closing and opening of said shunt connection

12. A method for the treatment of thrombosis in a patients extremity comprising the following steps:
- connecting the internal blood circulatory system of said extremity to an extra-corporeal circulation;
- isolating the extremity from the rest of the patient's circulation while

maintaining an extracorporeal circulation in said extremity;
- adding a thrombolytic agent.

13. A method as recited in claim 12 further comprising the following step
- catheterising the patient using Seldinger technique

14. A method as recited in claim 13 further comprising the following step
- adding a therapeutic liquid to a fluid in said extracorporal circulation, said fluid being blood or a therapeutic liquid or a mixture thereof

15. A method as recited in claim 14 further comprising the following step
- oxygenating the fluid

16. A method as recited in claim 15 further comprising the following step
- warming the fluid

17. A method as recited in claim 16 where said thrombolytic agent is so effective or present in such high concentration that it could cause haemorrhage or other side effect injuries if said liquid entered the blood circulation of the brain or other sensitive organ.

18. An apparatus for treatment of a patient's extremity characterised in that said apparatus comprises:
- a tourniquet-shaped compressing means (205) having a predetermined height (h)
- an incompressible arterial catheter (202) having an elongated section (305) that is reinforced to withstand an outside pressure and where said section have a length (L) that is greater than the height (h) of the compressing means (305)
- an incompressible venous catheter (201) likewise having an elongated section (305) that is reinforced to withstand an outside pressure and where said section have a length (L) that is greater than the height (h) of the compressing means (305)

19. An apparatus for treatment of a patient's extremity characterised in that said apparatus comprises:
- a tourniquet-shaped compressing means (205) having a given height (h)

20. An apparatus for treatment of a patient's extremity characterised in that said apparatus comprises:
- an incompressible arterial catheter (202) having an elongated section (305) that is reinforced to withstand an outside pressure and where said section have a length (L) that is long enough to keep a passage througt the catheter open when said catheter is subjected to said outside pressure.
- an incompressible venous catheter (201) likewise having an elongated section (305) that is reinforced to withstand an outside pressure and where said section have a length (L) that is long enough to keep a passage througt the catheter open when said catheter is subjected to said outside pressure

21. A catheter (202) charcterised by a reinforced elongated section (305), and where said section (305) have a length (L) that is long enough to keep a passage through the catheter open when said catheter (202) is subjected to an outside pressure over a part of said length (L).

22. A catheter (202) as recited in claim 21, having a first (301) and a second end (303), said second end being devised to being connectable to a fluid circulation loop.

23. A fluid circulation loop, for use in an apparatus for treatment of a patient's extremity, comprising a number of tubes an devised to being connectable to a catheter (201) at one end and to another catheter (202) at another end.

24. The fluid circulation loop as recited in claim 23 further comprising shunt means (150) for facilitating priming and de-airing of the fluid circulation loop and the catheters.

25. The fluid circulation loop as recited in claim 24 where said shunt means is a connection between a venous and an arterial part of the fluid loop and where said connection is provided with a valve.

26. A venous reservoir (180) for use in an apparatus for treatment of a patient's extremity.

27. A pump (101), for use in an apparatus for treatment of a patient's extremity, said pump having a motor with a rotor and having a tube receiving area provided with tube fixing means being applicable to a fluid circulation loop of said apparatus.

28. An oxygenator (108), for use in an apparatus for treatment of a patient's extremity, said oxygenator being connectable to a fluid circulation loop and devised for oxygenating a fluid passing through said loop.

29. A heat providing means (103), for use in an apparatus for treatment of a patient's extremity, said means being devised to add caloric energy and control the temperature of a circulating fluid.

30. A control unit (199, 401) comprising a input unit (410) for a number of input signal lines, a processor (412), a memory unit (418) provided for storing computer program instructions for instructing the processor (412) and for storing control parameters input from a keyboard (416) and a output unit (411) for a number of control lines, and devised for controlling a number of process parameters including fluid pressure and temperature, oxygen saturation, and the flow speed of said fluid.

31. The control unit (199, 401) as recited in claim 30 further comprising a display (414) devised for displaying trend curves and the level of fluid in a venous reservoir and time of treatment.

32. The control unit (199, 401) as recited in claim 31 further comprising computer program instructions for controlling heating means (103) and an oxygenator means (108) and electronically manoeuvrable valves.

ABSTRACT

A apparatus for treatment of a patient's extremity using a therapeutic fluid, said apparatus comprises:

- an incompressible arterial catheter (202);
- an incompressible venous catheter (201);
- a fluid circulation loop, having a first end (132) connectable to the arterial catheter (202), and a second end (140) connectable to the venous catheter (201);
- pump means (101) for providing circulatory energy substituting heart function;
- compressing means (205) for compressing a proximal end of the extremity so that essentially all vessels passing a cross section of said extremity become compressed.

The compressing means(205) will prevent the therapeutic fluid from leaving the extremity and enter the rest of the circulatory system of the patient, decreasing the risc of haemorrhage or other side effects in sensitive areas of the body, such as the brain.

The apparatus will be well suited for treating acute thrombosis.

(Fig. 1 and 2)

6 40 6119689

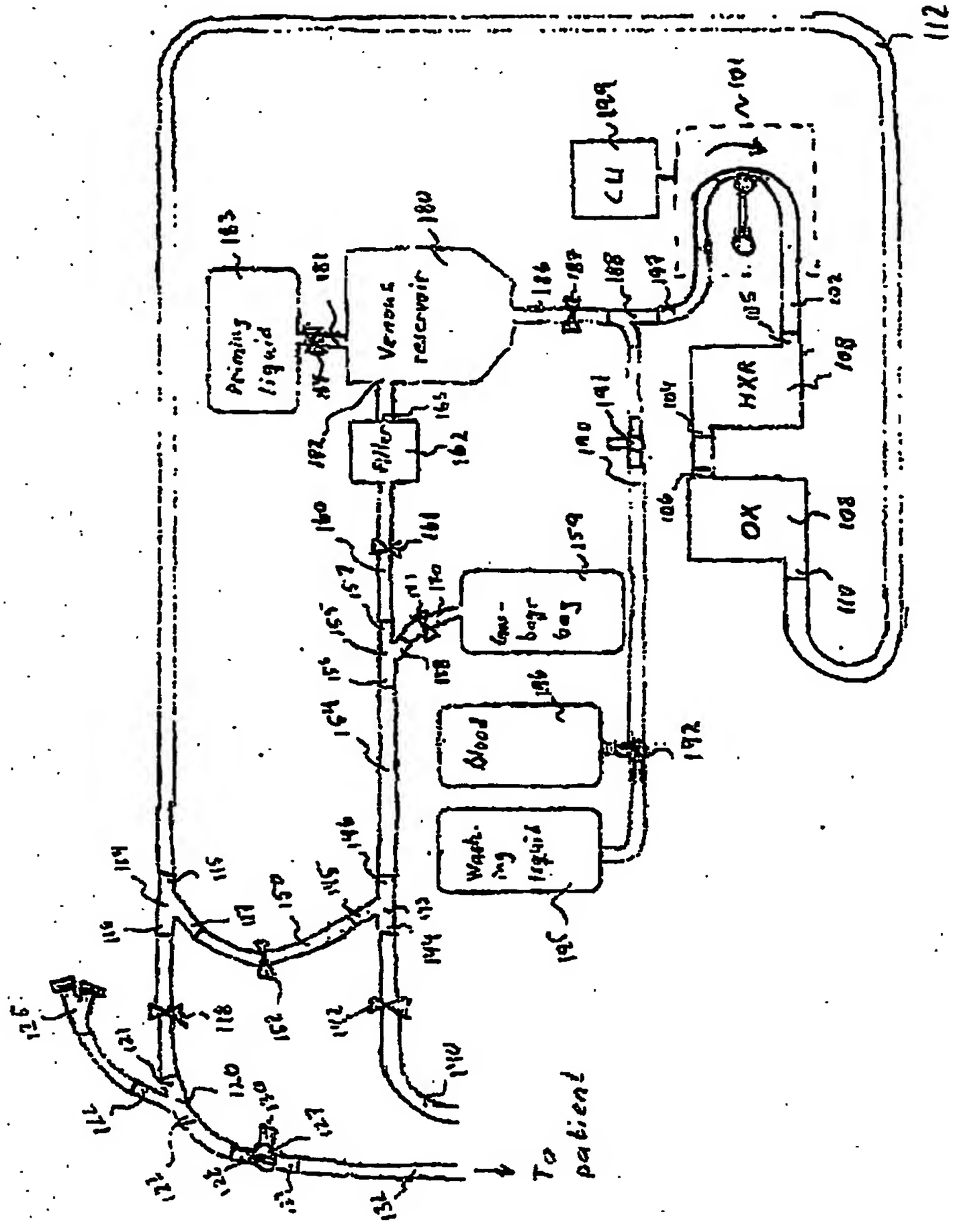

Fig. 1

2/4

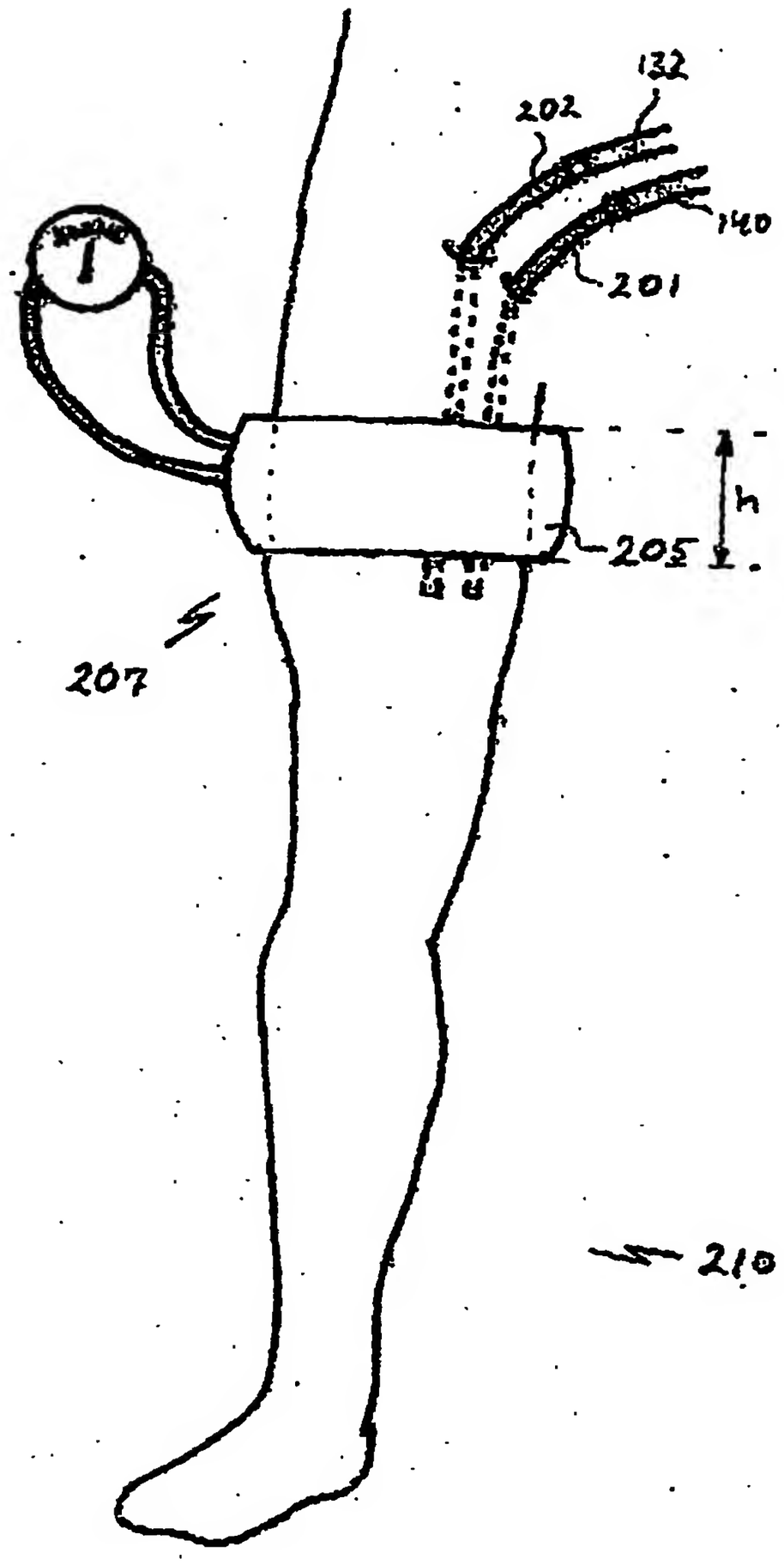

Fig. 2.

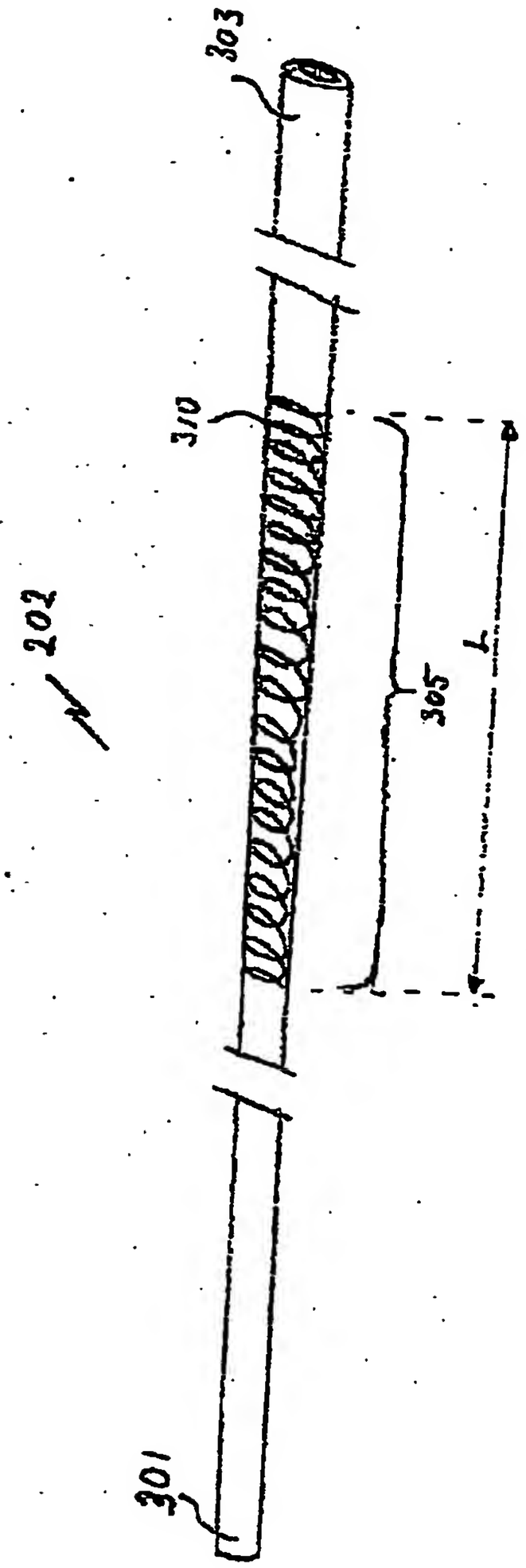

Fig. 3

4/4

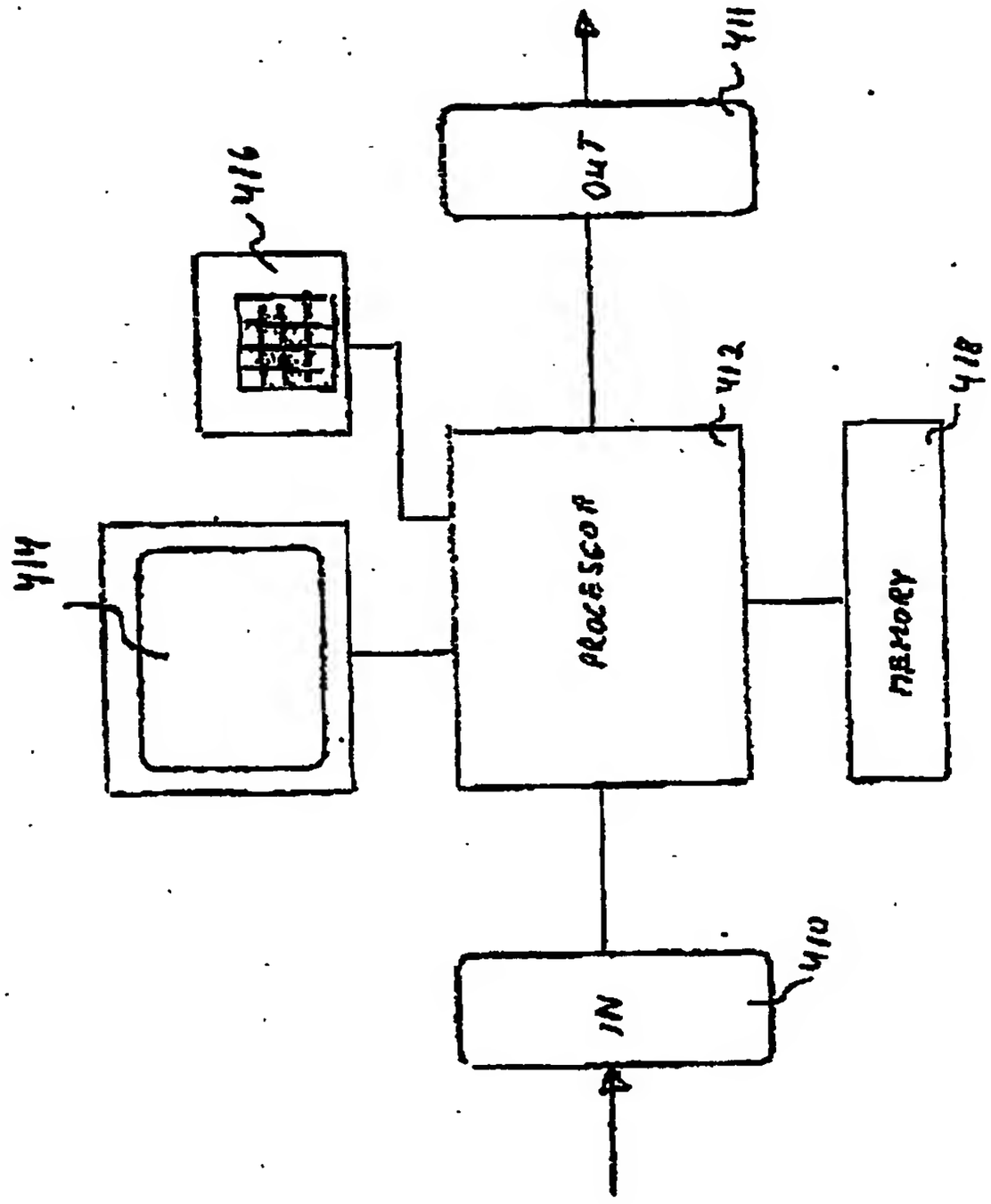

Fig 4